Remarks

The Applicant respectfully requests that the application be reconsidered in view of the above amendment and following remarks.

The invention relates to agents such as Ctx, Etx, CtxB, EtxB, antibodies, and derivatives of antibodies that bind to GM1 or modify a GM1-associated activity which are employed to treat asthma, allergic cough, allergic rhinitis and conjunctivitis, atopic eczema and dermatitis, uticaria, hives, insect bite allergy, dietary allergy and drug allergies, and contact sensitivity to plant allergens. A preferred embodiment provides treatment for asthma.

Claims 49, 53-56, 59-64 and 66-82 stand rejected as not being reasonably enabled commensurate in scope with the claims. These rejections are respectfully traversed. Applicant has amended the specification and the independent claims 49, 56, 61, & 76 such that they are supported by an enabling disclosure. The scope of the amended claims is commensurate with the specification. More specifically, "mutant or derivative thereof" has been removed from the claims. Accordingly the Examiner's objection that any "mutant" and "derivatives" of Etx, Ctx, EtxB, CtxB do not have a structure are obviated. Secondly, the specification at page 20 has been amended to specify the "allergic conditions" or "hypersensitivity conditions" as the conditions listed in the Application at the time of filing. No new matter has been added to this patent application. The scope of the claims is consistent with the disclosure of the specification. The Applicant has previously provided in vivo data as evidence of enablement for EtxB for treating asthma, and it is respectfully submitted that the amended claims are supported by the amended specification and further supported in the declaration of Neil Andrew Williams. Reconsideration and withdrawal of the rejections is respectfully requested.

Claims 49, 53-56, 59-64 and 66-82 were rejected as containing subject matter, which was not described in the specification. Independent claims 49, 56, 61, & 76 have

been amended, and reference to any "mutant or derivative thereof" has been removed from the claims. Accordingly the Examiner's objection that any "mutants" or "derivatives" of Etx, Ctx, EtxB, CtxB do not have a structure, or functions are obviated. Applicant respectfully submits that the written description accurately describes the claimed invention. Reconsideration of the claims as amended is requested.

Claims 49, 53, 55, 56, 59, 61-63, 71, 76, 79 and 80 stand rejected as obvious in light of WO 95/10301 in view of WO 97/02045 or Nashar et al.(1996). These rejections are respectfully traversed, and Applicant respectfully requests that the Examiner reconsider the rejection.

WO 95/10301 relates to an immunological tolerance-inducing agent comprising a mucosabinding molecule linked to a specific tolerogen. Further, a method of inducing immunological tolerance in an individual against a specific antigen, including hapten is described.

WO 97/02045 relates to the use, as an agent in the treatment or the prevention of autoimmune disease, of 1) an agent having GM-1 binding activity, other than by Ctx or Etx or the B subunits of Ctx and Etx; or 2) an agent having an effect on GM-1 mediated intracellular signally events, but no GM-1 binding activity. These agents may also be used in the treatment of human T cell leukemia.

Nashir relates to an assay method of measuring levels of various cytokines and antibodies associated with an immune response. The disclosure relates to a comparison between EtxB and a mutant EtxB (G33D) which does not bind to the GM-1 receptor.

The Examiner has taken the position it would have been obvious at the time the invention was made to substitute the agent such as LTB or CTB as taught by WO 95/10301 for the derivative or mutant such as EtxB(G33D) or agent such as EtxB as taught by WO97/02045 or the Ctx and EtxB (G33D) as taught by Nashir for a method

for treating a subject for allergic or hypersensitivity condition as taught by WO 95/10301 publication. The Examiner has taken the position that from the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a "reasonable of success" in producing the claimed invention.

The applicant respectfully disagrees with the Examiner for the following reasons:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See MPEP 2143.

As stated above, the claimed invention relates to agents that bind to GM1 or modify a GM1-associated activity which are employed to treat asthma, allergic cough, allergic rhinitis and conjunctivitis, atopic eczema and dermatitis, uticaria, hives, insect bite allergy, dietary allergy and drug allergies, and contact sensitivity to plant allergens.

With respect to Claim 49, an independent claim from which claims 53, 55 depend, the prior art references (or references when combined) fail to teach or suggest all the claim limitations. Independent claim 49 of the claimed invention requires, among other things, the step of administering to the subject an effective amount of an agent that is selected from the group consisting of Etx, Ctx, EtxB, CtxB, antibodies, and derivatives of antibodies, that bind to GM1. Consequently, an effective amount of agent must be utilized to effectively treat a subject in need thereof for "allergic or hypersensitivity condition." Allergic conditions is defined on page 20 to mean asthma, allergic cough, allergic rhinitis and conjunctivitis, atopic eczema and dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat, etc.) and drug allergies. The term "hypersensitivity condition" means contact hypersentisitivy induced by insect,

animal, plant, or microbial allergens. Although the Examiner has correctly taken the position that WO 95/10301 differs from the teachings of this reference in that the agent is not coupled to an antigen, the Applicant respectfully submits that this is not the only difference between the cited prior art and the claimed invention. WO 95/10301 does not disclose administering an effective amount of agent to solve the problems of treating allergic or contact hypersensitivity conditions. Accordingly, this limitation is not disclosed in the reference.

Similarly, WO97/02045 fails to teach the step of administering to the subject an effective amount of an agent that is selected from the group consisting of Etx, Ctx, EtxB, CtxB, antibodies, and derivatives of antibodies, that bind to GM1. The Examiner has taken the position that this reference discloses administering to the subject an effective amount of an agent such as a B subunit of E.coli heat -labile enterotoxin or a derivative of EtxB . . . and an antigen such as OVA, . . . in a mixture. The reference is particularly concerned with treating autoimmune disease. Autoimmunity being used to describe the mechanism by which the body generates an immune response to self-antigens. The present invention solves the problem of treating subjects for allergic conditions as defined on page 20, meaning asthma, allergic cough, allergic rhinitis and conjunctivitis, atopic eczema and dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat, etc.) and drug allergies. The present invention further solves the problem of treating subjects in need thereof from "hypersensitivity condition" which means contact hypersentisitivy induced by plant allergens. It is respectfully submitted that WO97/02045 does not disclose the required claim limitation of administering an effective amount of agent to solve the problems of allergy or contact hypersensitivity. Accordingly, limitation in claim 49 is not disclosed in the reference.

Similarly, Nashir fails to teach or suggest administering to the subject an effective amount of an agent that is selected from the group consisting of Etx, Ctx, EtxB, CtxB, and mutant G33D, that bind to GM1. The claimed invention solves the problem of treating subjects in need thereof for allergic conditions as defined on page 20. The claimed

invention further solves the problem of treating subjects in need thereof from "hypersensitivity condition" which means contact hypersentisitivy induced by plant allergens. Nowhere does Nashir teach or suggest an effective amount of adminstering these specific agents to treat solve the problems in developing a treatment for a subject in need thereof for allergic or hypersensitivity conditions as required by the claims of the present invention.

A reasonable expectation of success, standing alone, is not enough to show obviousness. It is respectfully submitted that the Examiner is suggesting that the invention was obvious to try. Since each and every limitation of claim 49 is not disclosed in the prior art, claim 49 is not obvious.

Claim 56 stands rejected as obvious in light of WO 95/10301 in view of WO 97/02045 or Nashar et al. (1996). The rejection is respectfully traversed, and Applicant respectfully requests that the Examiner reconsider the rejection.

As stated above, the present invention solves the problem of treating allergic subjects in need thereof for conditions as defined on page 20 meaning asthma, allergic cough, allergic rhinitis and conjunctivitis, atopic eczema and dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat, etc.) and drug allergies. The claimed invention further solves the problem of treating contact hypersentisitivy induced by various allergens. Nowhere do the cited references disclose administering to a subject for an allergic or hypersensitivity condition comprising administering to the subject an effective amount of an agent that is selected from the group consisting of Etx, Ctx, EtxB, $CtxB_1$ antibodies, and derivatives of antibodies, that bind to GM1, wherein the agent is administered with an antigen/allergen and is not coupled to an antigen in order to solve the problems of the claimed invention. The prior art does not teach that the technology disclosed therein is applicable to the treatment of allergic conditions and hypersensitivity conditions as disclosed by the present invention. Ac-

cordingly, claim 56 is not obvious in light of WO 95/10301 in view of WO 97/02045 or Nashar et al.(1996).

The Examiner has objected to claims 54, 60, 61, 64, 66-69, 70, 72, 73, 74, 75, 77, 78, 81 and 82 as obvious in light of WO 95/10301, WO/97/02045 or Nashar and further in view of *Roitt et al.* and *Patterson et al.* The rejection is respectfully traversed, and Applicant respectfully requests that the Examiner reconsider the rejection.

In light of the amendments made herein, it is respectfully requested that the Examiner reconsider the response of December 12, 2002. Roitt *et al.* describes hypersensitivity in general terms. Patterson *et al.*, attempted to determine if human peripheral blood lymphocytes cultured in vitro could be used to study the pharmacological effect of agents on IgE production. The prior response to the previous objections based on these references is hereby incorporated by reference. Alone or in combination, the cited references do not solve the problem of the claimed invention by providing a method of <u>treating</u> subjects in need thereof for allergic conditions as defined on page 20 of the specification meaning asthma, allergic cough, allergic rhinitis and conjunctivitis, atopic eczema and dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat, etc.) and drug allergies. They do not teach a solution for treating contact "hypersensitivity condition" induced by allergens. These refrences would not be consulted by a skilled worker looking for ways to provide an <u>effective amount</u> of agent in a new treatment for subjects in need of treatment for allergy and hypersensitivity. Accordingly, the claim 61 is not obvious.

The arguments made above with respect to WO 95/10301, WO/97/02045 or Nashar are herein incorporated by reference in response to the instant objection. Since Applicant maintains that claim 76 is not obvious, dependent claims 77-82 are not obvious.

The Examiner has objected to claims 49, 53, 55, 56, 59, 61-63, 71, 76, 79 and 80 as unpatentable over Tamura in view of WO/97/02045 or Nashar as applied to claims 49, 53, 55, 56, 59, 61-63, 71, 76, 79 and 80. The rejection is respectfully traversed, and Applicant respectfully requests that the Examiner reconsider the rejection in light of the amendments made to each independent claim.

As previously indicated on the record, the experimental results previously provided by Applicants' research group in the WO 97/02045 and Nashar and Tamura *et al.* do not suggest Applicants' claimed invention. On the contrary they point away from the invention by suggesting that GM1 binding agents would not find use in the treatment of allergic/hypersensitivity conditions.

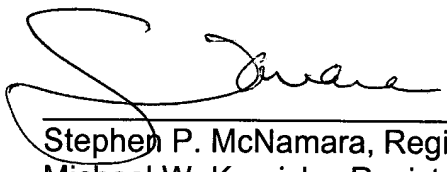
In light of the amendment to the claims, deleting "mutants and derivates", and the amendment to the specification clarifying the specific allergic conditions, Applicants urge reconsideration of the declaration by Dr. Neil Andrews Williams in demonstrating that claims 49, 56, 61, and 76 are not obvious.

The Examiner has objected to claims 54, 60, 61, 64, 66-69, 70, 72, 73, 74, 75, 77, 78, 81 and 82 as unpatentable over Tamura in view of WO/97/02045 or Nashar as applied to claims 49, 53, 55, 56, 59, 61-63, 71, 76, 79 and 80, and further in view of Roitt *et al.*

The Applicant respectfully submits that each of the claims objected to in the instant objections are dependent claims and therefore not obvious for the reasons their respective independent claims are not obvious as stated above.

In view of the foregoing amendments to claims 49, 56, 61, and 76 and remarks, it is urged that this application is in condition for allowance. If the Examiner has any questions regarding this Response, the Examiner is invited to call Michael Krenicky at (203) 324-6155. Early favorable action is respectfully requested.

Respectfully submitted,



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